IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
Guarna et al..	)	Art Unit:1617
	)	
Serial No.: 10/518,689	)	Examiner: Ramachandran Umamaheswari
	)	
Filed: December 17, 2004	)	
	)	

For: **PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF DISEASES RELATED TO NEUROTROPHINES**

DECLARATION UNDER CFR 1.132

I, Antonio Guarna, say that:

1. I am an Italian citizen residing in Seravezza, Via Zingola 943, (Lucca) ITALY

2. I am familiar with the English language

3. I am co-inventor in the US Patent Application 10/518,689

4 I further declare that:

I was born in Catanzaro 10 February 1950. Nationality: Italian.
Since 2000 I am full Professor of Organic Chemistry, University of Florence, Italy.
1985-2000 I was Associate Professor of Organic Chemistry and of Stereochemistry, University of Florence
1978-1985: I was Assistant Professor of Organic Chemistry,.
1974-78 I get Fellowships from National Research Council of Italy and Ministero Pubblica Istruzione.
1973 December: I get the Master Degree in Organic Chemistry, (full marks and honours) at University of Florence.
My scientific activity is focussed on medicinal chemistry and synthetic organic chemistry. Recent researches are: Stereoselective synthesis of biologically active heterocycles; Study on substrates and inhibitors of steroid metabolism enzymes. Synthesis of new molecular scaffolds and their application for drug discovery. Labelling of biologically active compounds with stable or radioactive isotopes. Synthesis of molecules active against CNS's receptors. Synthesis of new molecules for treatment of neurodegenerative diseases. Synthesis of peptidomimetics and their immobilization on solid phase. These researches were developed also in collaboration with pharmaceutical companies for studies on synthesis, molecular modelling and biochemical evaluation of new chiral heterocycles.
I am author of 138 publications, 7 reviews and 12 patent applications.
Research activity
I am membership of Italian Chemical Society, Division of Organic Chemistry, and of American Chemical Society, Division of Organic Chemistry.
Since 2005 I was Coordinator of the Master on "Innovative Synthetic methods in Organic Chemistry". In 2006 I was Director of the Interdepartmental "Laboratory of Design, Synthesis and Study of Biologically Acive Heterocycles (HeteroBioLab)" at University of

Florence. Since November 2006 I am Director of the Department of Organic Chemistry "Ugo Schiff", University of Florence Italy.

5. I further declare that the present Patent application refers to pharmaceutical compositions that possess pharmaceutical properties (in particular for the treatment of diseases in which the neurotrophine functions are involved in defect).

I have been informed that during the examination procedure in front of the USPTO it was objected that amide precursors of BTAa(O) compounds described in my previous scientific publications could be considered as anticipating the subject matter of the Application since in such works ethanol or aqueous solution of said compounds are described and these solution are considered by the Examining authorities as pharmaceutically acceptable excipients or diluents. In connection with this objection the following should be considered.

6. Ethanol or ethanolic solutions (as well as aqueous solutions) are cited in the two documents cited as prior art Guarna et al. 1999 and Cini et al. 2002 only as solvents used in the preparation of the compounds and therefore are not suitable for any pharmaceutical use either on humans or on animals.

7. Ethanol is a solvent employed in a reaction of compound 8 to produce compound 16, as described in Scheme 3 on page 875 of Cini (and on page 878). The ethanol employed to dissolve compound 8 for this reaction was not of pharmaceutically acceptable quality. Accordingly, the solution of compound 8 in ethanol as employed in Cini is not a pharmaceutical composition.

In addition, ethanol is cited with reference to the preparation of compound 21 in Cini et al. (page 879):
(-)-Methyl (1*S*,2*R*,5*S*,6*R*)-3-Benzyl-2*endo*-hydroxymethyl-7,8-dioxa-3-azabicyclo[3.2.1]octane-6*exo*-carboxylate (21): BH_3·Me_2S in THF (10 M, 23.5 µL, 0.235 mmol) was added at 0 °C to a solution of **18** (70 mg, 0.242 mmol) in dry THF (2 mL). The solution was stirred at room temperature for 5 h, ethanol (2 mL), NaOH (30 µL), and 35% H_2O_2 (30 µL) were then added successively, and the resulting mixture was heated at 50 °C for 1 h.

In synthesizing compound 21, compound 18, that is belonging to the class of BTA(O) amide intermediates, is dissolved in THF (which is not a pharmaceutically acceptable solvent or diluent) and treated with a mixture of ethanol, sodium hydroxide and H_2O_2 which are reagents necessary to destroy the excess of the reagent BH_3.Me_2S. This mixture of organic solvents and reagents is also not a pharmaceutically acceptable solvent or diluent for this compound.

8. In Guarna et al. 1999, the N-protected R-BTAa-(O)-OMe derivatives were easily transformed into the corresponding acids either under acid conditions with aqueous 2 N HCl or basic conditions with KOH/MeOH. As described on page 362, compound 15 is prepared from compound 2: **(1*R*,5*S*,7*R*)-3-(*p*-Methoxybenzyl)-2-oxo-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-*exo*-carboxylic Acid (15).** To a suspension of **2** (50 mg, 0.163 mmol) in water (10 mL) was added under stirring a 1 M aqueous solution of NaOH (10 mL).

In this case, compound 2 is in a water suspension. The water employed to suspend compound 2 was not of pharmaceutically acceptable quality. Accordingly, the suspension of compound 2 in water in Guarna et al. 199 is not a pharmaceutical composition.

9. The word "aqueous" is present in the whole document Cini et al. 2002 only 6 times but in all the cases is referred to salt solutions for the work-up treatment of reaction mixtures and not directly to dissolve the amide intermediates BTA(O).

The word "water" is present in the whole document Guarna et al. 1999 13 times, but it is not referred to a solvent for amide intermediates BTA(O), but only as solvent for salt solutions used for work-up of reaction mixtures.

The word "water" is present in the whole document Cini et al. 2002 8 times, but it is not referred as a solvent for amide intermediates BTA(O), but only as solvent for salt solutions used for work-up of reaction mixtures.

For example in preparation of intermediate BTA(O) 8 in Cini et al. 2002, the authors referred that:

The organic phase (containing **8**) was washed with saturated aqueous $NaHCO_3$ and **water**, and dried with Na_2SO_4. After evaporation of the solvent (organic phase), the crude product was purified by chromatography (EtOAc/petroleum ether, 1:2, *Rf* 5 0.26), yielding **8**... (page 877)

Thus from these examples is evident that the prior art does not teach anything about the use of ethanol or water as pharmaceutically acceptable solvent or diluent.

10. I further declare that all the statements of my own knowledge are true and that all the statements made on information and belief are believed to be true and further that these statements were made with the knowledge that wilful false statement and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statement may jeopardize the validity of the application o of any patent issuing thereon.

Firenze,

SIGNATURE

Prof Antonio Guarna